

# Serum Lp(a) lipoprotein concentration and outcome of thrombolytic treatment for myocardial infarction

Anthony D MBewu, Paul N Durrington, Michael I Mackness, Linda Hunt, Wajdi H Turkie, John E Creamer

## Abstract

**Background**—Lp(a) lipoprotein has structural homology with plasminogen and has been shown to inhibit plasminogen activation in vitro.

**Objective**—To determine whether the serum concentration of Lp(a) lipoprotein present when streptokinase was given in acute myocardial infarction influenced the outcome as judged by electrocardiographic methods.

**Patients and design**—Serum Lp(a) lipoprotein concentration was measured in 135 consecutive patients admitted with a diagnosis of acute myocardial infarction who received streptokinase treatment. Recovery from myocardial injury was assessed by the reduction in the sum of ST segment elevation measured from the J point (STJ) in the electrocardiogram immediately before streptokinase was given compared with that three hours later.

**Results**—The serum Lp(a) lipoprotein concentrations were measured within 12 hours of the onset of symptoms of myocardial infarction and were higher than in healthy reference populations. Recovery from myocardial infarction could be assessed from the STJ in 116 patients (86% of the series). Those in whom it could not had bundle branch block, left ventricular hypertrophy, did not survive three hours, or had started intravenous nitrate treatment or some other clinical procedure before or at the time the second electrocardiogram was to be recorded. Patients with reductions in STJ after streptokinase that were  $> 4$  mm (the median decrease) had mean (range) serum Lp(a) lipoprotein concentrations of 41.0 (0.8–220) mg/dl and those with a smaller reduction in STJ had concentrations of 29.1 (1.7–151) mg/dl. The difference was not statistically significant.

**Conclusion**—In this study Lp(a) lipoprotein concentration did not significantly influence the outcome of thrombolytic treatment with streptokinase.

(Br Heart J 1994;71:316–321)

Thrombolysis is well established in the treatment of myocardial infarction<sup>1–3</sup> and has been shown to increase patency of the infarct related coronary artery,<sup>4</sup> reduce the size of the

myocardial infarct,<sup>5</sup> preserve left ventricular dimensions and function,<sup>6,7</sup> and reduce both early and late mortality.<sup>8,9</sup>

The Lp(a) lipoprotein is widely held to be an important risk factor in coronary heart disease. High serum Lp(a) lipoprotein concentrations are associated with an increased prevalence of angina pectoris, myocardial infarction, and coronary artery disease assessed angiographically.<sup>10–12</sup> The Lp(a) lipoprotein has close structural homology with plasminogen<sup>13</sup> and can impede fibrinolysis at the surface of cultured human endothelial cells.<sup>14</sup> Enormous doses of thrombolytic agent are used in the treatment of myocardial infarction, however, which might be predicted from in vitro studies, to overwhelm any competition by Lp(a) lipoprotein.<sup>15</sup> None the less in vivo similar kinetic considerations may not apply locally at a thrombosis in a coronary artery and the possibility remains that Lp(a) lipoprotein might impede plasminogen activation or compete with plasminogen and plasmin treatment impeding breakdown of the fibrin clot.

We therefore investigated the influence of the prevailing serum concentration of Lp(a) lipoprotein on the clinical outcome of acute myocardial infarction treated with streptokinase.

## Patients and methods

### PATIENTS

Approval for this study was obtained from the Clinical Ethics Committee of our hospital, and all patients participating gave their informed consent. All patients admitted to the coronary care unit with a diagnosis of acute myocardial infarction were treated with streptokinase unless there were specific contraindications—namely, more than 12 hours since the onset of continuous chest pain; confirmed peptic ulcer within the previous six months; current symptoms suggestive of peptic ulcer; cerebrovascular accident within the past 12 months; bleeding diathesis; recent surgery (less than three months); streptokinase treatment within the past six months.

Between September 1989 and February 1991 162 consecutive patients were admitted to our coronary care unit with a diagnosis of definite myocardial infarction and no contraindication to streptokinase. Two died immediately leaving 160 who were treated with intravenous streptokinase (1.5 MU over one hour, Hoechst Streptase or Kabi Vitrum Kabikinase). Venous blood was taken

University of Manchester  
Department of Cardiology  
A D MBewu  
W H Turkie  
J E Creamer

University of Manchester  
Department of Medicine  
P N Durrington  
M I Mackness

University of Manchester Faculty of Medicine  
Computational Group, Manchester Royal Infirmary  
Linda Hunt

Correspondence to:  
Dr Paul N Durrington,  
The University Department of Medicine, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL.

Accepted for publication  
1 November 1993.

immediately before the infusion of streptokinase for the determination of serum Lp(a) lipoprotein and plasma fibrinogen. Serum Lp(a) lipoprotein values before streptokinase were obtained for 135 patients (eight declined to participate, and in 17 cases no satisfactory sample was obtained for measurement generally because the clinical team on duty started the streptokinase infusion before obtaining blood for the study or because of clinical urgency). In a subset of patients serum Lp(a) lipoprotein and fibrinogen were also measured at the end of the streptokinase infusion. We include the fibrinogen results. There was no change in serum Lp(a) lipoprotein concentrations after the infusion of streptokinase.<sup>16</sup>

Twelve weeks after the myocardial infarction, patients were seen in our clinic by ADM to check for recurrent angina, heart failure, changes in medication, blood pressure, weight, and height. On this occasion a fasting blood sample was obtained after the patient had fasted since 22 00 the previous night. The serum cholesterol, triglyceride, high density lipoprotein cholesterol, and apolipoprotein B results presented here were obtained from this sample. In a subset of patients it was shown that these values were not significantly different from those obtained on admission.<sup>16</sup> Seventeen (12.6%) of the 135 patients with Lp(a) lipoprotein values before streptokinase had died by the time of the 12 week visit. Data for some variables are incomplete for this reason.

#### CARDIOLOGICAL INVESTIGATION

The diagnosis of myocardial infarction was based on a history of typical, prolonged (>30 minutes) chest pain, plus diagnostic electrocardiographic changes of  $\geq 2$  mm of ST segment elevation in at least two contiguous precordial leads on the admission electrocardiogram or  $\geq 1$  mm of ST elevation in two or more inferior electrocardiographic leads, plus a diagnostic rise in serum cardiac enzymes.

The electrocardiogram on admission to hospital was taken by trained nurses in the casualty department or coronary care unit and venous blood was taken at that time for estimation of serum Lp(a) lipoprotein. Streptokinase was given as soon as possible once the diagnosis was made and the patient was given aspirin (150 mg) to chew (provided there was no history of allergy to aspirin). No patients had an allergy to aspirin but 10 of the 153 (6.5%) patients did not receive aspirin because of a history of peptic ulcer or dyspepsia.

A second electrocardiogram was performed three hours after starting streptokinase. This was compared with the electrocardiogram recorded immediately before the streptokinase. Changes in the sum of ST elevation in all 12 leads of the electrocardiogram at the J point (STJ) and 60 ms after the J point were measured. Changes in the degree of ST elevation in the lead with the maximum ST elevation (STmax) at the start of streptokinase infusion were also measured. The decline in the sum of ST elevation in the electrocardio-

gram has previously been shown to correlate well with recovery from myocardial injury and reperfusion of the infarct-related artery.<sup>17-19</sup> Of the 135 patients studied 116 had electrocardiograms that could be analysed. Six could not because of left or right bundle branch block or left ventricular hypertrophy, four could not because the patients died before the second electrocardiogram, and nine were excluded because intravenous nitrate infusion had been given to the patients in the interval between the first and second electrocardiogram or the second electrocardiogram could not be recorded at three hours because the patient's condition demanded some other more urgent clinical procedure at the time.

Electrocardiograms were performed daily during the 48 hour or longer stay on the coronary care unit and again before discharge from hospital, and the clinical progress of the patient was monitored by one of us. The electrocardiogram recorded before discharge from hospital was used to calculate a Selvester score, which correlates well with the size of the myocardial infarction.<sup>20 21</sup>

Sixty five of the patients had coronary angiography at a median of six days after thrombolysis, and these films were used to check for patency of the infarct related artery with a protocol from the Thrombolysis in Myocardial Infarction Study.<sup>4</sup> Coronary angiography was performed in all patients under the age of 50 for men and 65 for women ( $n = 24$ ) and in patients with recurrent chest pain after myocardial infarction ( $n = 39$ ), or for other clinical indications ( $n = 2$ ), unless there were contraindications such as massive myocardial infarction with poor ensuing left ventricular function.

The films were independently scrutinised by two experienced angiographers on different occasions to assess the patency of the infarct related artery.<sup>4</sup> Both observers were unaware of the clinical state or blood results of the patients.

#### LABORATORY METHODS

High density lipoprotein cholesterol was measured by the managanese/heparin precipitation method.<sup>22</sup> Serum total cholesterol was determined enzymatically (reagent supplied by Diamed, Murten, Switzerland) and serum triglycerides by the glyceryl phosphate oxidase-peroxidase-aminophenazone method (Boehringer Mannheim, Mannheim, Germany). Within batch coefficients of variation for cholesterol and triglyceride assays were 1.5% and 2.1% respectively. Our laboratory participates in the national quality control scheme. Apolipoprotein B was determined by immunonephelometry with the Beckman Array (Beckman Instruments, Palo Alto, California, USA). The antiserum to apolipoprotein B was supplied by Beckman. The method was repeatedly calibrated against a secondary serum standard, the apolipoprotein B concentration of which was determined by immunoelectrophoresis with a primary standard of lipoprotein of density 1.040–1.053 g/ml isolated by ultracentrifugation.<sup>22</sup>

Table 1 Characteristics of patients on admission to the coronary care unit (mean (SD)) or median (range))

	All patients	Patients whose ST change could be measured	Patients with coronary angiograms
No (M:F)	135(106:29)	116(91:25)	62(53:9)
Age (y)	58(32-82)	59(32-82)	54(34-71)
Serum cholesterol (mmol/l)	6.81(1.52)	6.74(1.54)	6.84(1.52)
Serum triglycerides (mmol/l)	2.23(0.61-8.64)	2.22(0.61-8.64)	2.25(0.90-8.17)
Serum HDL cholesterol (mmol/l)	0.9(0.35)	0.91(0.35)	0.91(0.40)
Serum apolipoprotein B (mg/dl)	113(31)	111(31)	113(32)
Serum Lp(a) lipoprotein (mg/dl)	34.0(0.8-220.0)	34.7(0.8-220.0)	24.2(0.8-184.8)
Plasma fibrinogen (g/l)	3.26(1.11)	3.26(1.12)	3.29(0.94)
Smokers (%)	60	58	64
Previous MI (%)	18	18	18
Systolic BP (mm Hg)	140(33)	141(34)	136(26)
Diastolic BP (mm Hg)	86(21)	86(21)	87(16)
Quelet's index (Kg/m <sup>2</sup> )	26.1(3.9)	25.9(3.8)	26.9(3.9)

Complete data were available for Lp(a) lipoprotein and for > 85% of patients for other variables except HDL (76%), apolipoprotein B (73%), fibrinogen (53%), and Quelet's index (80%). HDL, high density lipoprotein, MI, myocardial infarction.

The Lp(a) lipoprotein was determined by a two site immunoradiometric assay (Pharmacia, Uppsala, Sweden) previously evaluated in this laboratory.<sup>10</sup> This method shows no cross immunoreactivity with plasminogen or with low density lipoprotein, and has a lower detection limit of 0.06 mg/dl. The method was calibrated in our laboratory against the standard provided by Pharmacia. The results were expressed as mg total protein in Lp(a) lipoprotein (apolipoprotein(a) and apolipoprotein B) per dl serum, after repeated comparisons of the results obtained with the standard and preparations of Lp(a) lipoprotein isolated from pooled serum by ultracentrifugation and affinity chromatography. The protein concentration of these was determined by a modification of the Lowry method. The within batch coefficients of variation for the apolipoprotein B and Lp(a) lipoprotein assays were 5.4% and 2.1% respectively. In all lipid and apolipoprotein assays quality control serum samples were included to ensure that between batch variation was within acceptable limits. Serum creatine kinase activity was measured in the routine clinical chemistry laboratory for three days after admission.

#### STATISTICS

The unpaired Student's *t* test was used to compare the means of the variables, which were normally distributed. Serum Lp(a) lipoprotein concentrations and coronary

artery disease (Selvester) scores were compared with the non-parametric Mann-Whitney U test. Qualitative variables with two categories (sex, number with previous myocardial infarction, family history of coronary heart disease, smokers, proportion of patients with occluded infarct related artery who have serum Lp(a) lipoprotein > 25 mg/dl, percentage of patients with serum Lp(a) lipoprotein greater or less than the median Lp(a) lipoprotein, and percentage of patients with STJ greater or less than the median STJ) were compared with the  $2 \times 2 \chi^2$  test or Fisher's exact test (if the numbers were small).

Correlations between variables were sought with Kendall's test. The Wilcoxon matched pairs test was used to compare Lp(a) lipoprotein before myocardial infarction and at 12 weeks after myocardial infarction. Two tailed tests are reported throughout.

## Results

### PATIENTS STUDIED

Table 1 shows the clinical characteristics of the patients. The patients tended to have high cholesterol and triglycerides and low high density lipoprotein cholesterol compared with typical values for a healthy British population. The serum Lp(a) lipoprotein values were high, the median value in healthy local people being 10 mg/dl.<sup>23</sup> The site of the myocardial infarction on electrocardiographic criteria was inferior in 48%, anterior in 45%, posterior in 4%, and lateral in 3%. The median (range) time between the onset of chest pain and the start of the intravenous infusion of streptokinase was three (0.5-14) hours.

### MORTALITY

Seventeen (12.6%) of the 135 patients investigated died during the next three months. The median (range) serum Lp(a) lipoprotein concentration immediately before streptokinase in those who died was 28.8 (1.7-85.0) mg/dl, which was not significantly different from those who survived (34.0 (0.8-220.0) mg/dl). There was no significant relation between serum Lp(a) lipoprotein concentrations and mortality within the first three months or heart failure treated within the first three days.

### ELECTROCARDIOGRAPHIC INDICES OF OUTCOME OF THROMBOLYTIC TREATMENT

When patients whose ST segment recovery exceeded the median rate were compared with those with rates below this value (table 2) there was a tendency for serum Lp(a) lipoprotein concentrations to be higher in patients whose ST segments returned rapidly towards the isoelectric line than in those in whom it was slower to return. This was so regardless of the measure of ST segment elevation used. The difference was not significant by two tailed tests, which we considered should be used because our original hypothesis was that high circulating Lp(a) lipoprotein at the time of streptokinase infusion might unfavourably affect its outcome.

Table 2 Serum Lp(a) lipoprotein concentrations (median (range)) in patients above and below median change in ST segment elevation over the three hours after the intravenous infusion of streptokinase

Change in ST segment elevation	No	Serum Lp(a) lipoprotein (mg/dl)	<i>p</i> value*
J point:			
< 4 mm	56	29.1 (1.7-151)	0.087
≥ 4 mm	60	41.0 (0.8-220)	
60 ms:			
< 4 mm	57	28.8 (1.7-215)	0.089
≥ 4 mm	59	39.9 (0.8-220)	
ST max:			
< 1.5 mm	48	26.8 (1.7-151)	0.083
≥ 1.5 mm	68	41.0 (0.8-220)	

\*Mann-Whitney test (two tailed)

Table 3 Characteristics of the 62 patients who had coronary angiography mean (SD) or median (range)

	Infarct related artery	
	Occluded	Patent
No (M:F)	17 (14:3)	45(39:6)
Age (y)	58(36-71)	52(34-70)
Previous myocardial infarction (%)	35	12*
Smokers (%)	65	64
Peak serum Creatine kinase (U/l)	1721(100-3954)	1430(239-6248)
Time interval between streptokinase and coronary angiogram (days)	6.0 (1-20)	6.0 (0-23)
Time interval between onset of symptoms and streptokinase (h)	3(1.25-11.00)	3(0.75-12.00)
Serum cholesterol (mmol/l)	6.68(1.99)	6.90(1.34)
Serum apolipoprotein B (mg/dl)	110(31)	114(33)
Serum triglyceride (mmol/l)	1.75 (0.9-4.94)	2.42(0.99-8.17)
Serum HDL cholesterol (mmol/l)	0.88(0.40)	0.93(0.40)
Serum Lp(a) lipoprotein (mg/dl)	28.8(4.4-96.6)	23.5(0.8-185)

\*p = 0.085. All differences are NS. Data are incomplete for cholesterol, triglycerides, high density lipoproteins, and apolipoprotein B, because some patients did not survive until 12 weeks (see methods).

There was no significant correlation between the serum Lp(a) lipoprotein concentration and size of the myocardial infarction assessed by electrocardiography.

#### CORONARY ANGIOGRAPHIC OUTCOME OF THROMBOLYTIC TREATMENT

The 62 patients selected to have coronary angiography were younger than the rest. They were also minimally more obese ( $p < 0.05$ ) but in most other respects their clinical characteristics were similar to the others. There were also no significant differences in serum Lp(a) lipoprotein concentrations or in other lipid or lipoprotein variables between patients with occluded and patent infarct related coronary arteries (table 3). There was a trend for higher coronary artery disease scores and a tendency for previous myocardial infarction in patients with occluded infarct related coronary arteries.

#### HAEMATOLOGICAL RESPONSE TO THROMBOLYTIC TREATMENT

Before the streptokinase infusion the mean (SD) plasma fibrinogen was 3.26(1.11) g/l ( $n = 71$ ) and three hours afterwards it was 0.67(0.45) g/l ( $n = 77$ ). The pretreatment plasma fibrinogen in patients with occluded infarct related coronary arteries (3.53(1.15) g/l;  $n = 9$ ) and the fibrinogen response to streptokinase (0.79(0.77) g/l;  $n = 10$ ) were not significantly different from those with patent arteries (3.19(0.84) g/l;  $n = 21$  and 0.74(0.56) g/l;  $n = 25$ ). Furthermore plasma fibrinogen concentration did not differ between patients with a  $> 4$  mm fall in ST segment elevation and those in whom it was  $\leq 4$  mm. There was no significant correlation between the change in plasma fibrinogen from zero to three hours after the start of streptokinase treatment and the serum Lp(a) lipoprotein concentration before streptokinase infusion (Kendall's tau = 0.106, NS).

#### CHANGE IN SERUM LP(A) LIPOPROTEIN CONCENTRATION AFTER MYOCARDIAL INFARCTION

Paired serum samples taken before streptokinase infusion and 12 weeks after myocardial

infarction were available for 84 patients. Median serum Lp(a) lipoprotein 12 weeks after myocardial infarction was 42.4 (0.8-210) mg/dl and before streptokinase was 30.2 (0.8-220) mg/dl. These values were of borderline significance ( $p = 0.053$ ).

#### Discussion

There is an enormous volume of case-control evidence linking serum Lp(a) lipoprotein concentrations and premature coronary heart disease.<sup>10-12</sup> Furthermore in European populations a parental history of coronary heart disease early in life is associated with increased serum Lp(a) lipoprotein concentrations in offspring.<sup>10,24</sup> Also in familial hypercholesterolaemia, in which risk of coronary heart disease is greatly increased, the serum Lp(a) lipoprotein concentration is raised.<sup>23,25</sup> Prospective studies are, however, less persuasive with one<sup>26</sup> supporting Lp(a) lipoprotein as a determinant of risk of coronary heart disease and two failing to do so.<sup>27,28</sup> In our investigation the median Lp(a) lipoprotein value within 12 hours of the onset of symptoms of acute myocardial infarction was more than three times that of a healthy British population.<sup>23</sup> It is likely that the Lp(a) lipoprotein value this early in the course of myocardial infarction reflected its premorbid concentration and our study thus supports the view that Lp(a) lipoprotein is predictive of myocardial infarction. There was a tendency for serum Lp(a) lipoprotein concentrations to be higher 12 weeks after myocardial infarction than immediately after it. Maeda and colleagues found no acute changes in serum Lp(a) lipoprotein concentrations in the week after myocardial infarction, but there was a rise in some patients during the second week.<sup>29</sup> In a study of similar design we confirmed the relative stability of serum Lp(a) lipoprotein in the week after myocardial infarction with greater variation in the concentrations in the second week.<sup>16</sup> It is thus possible that the increase at 12 weeks after myocardial infarction may reflect this late rise in some people.

The Lp(a) lipoprotein is distinguished from other lipoproteins by possessing an apolipoprotein, apolipoprotein(a), which is a mutation of plasminogen. It has a protease domain structurally similar to that of plasminogen, but is not activated to lyse fibrin by plasminogen activators. Furthermore in place of the short series of five kringles present in plasminogen, Lp(a) lipoprotein has a long series of kringles due to repetition of kringles homologous to the fourth kringle of plasminogen. The number of these repeats is determined by a single genetic locus and is responsible both for the genetic variation in the molecular mass of apolipoprotein(a) and largely for its circulating concentration.<sup>30</sup>

Because of its resemblance to plasminogen and its lack of activation by known plasminogen activating factors, Lp(a) lipoprotein seems an obvious candidate to inhibit fibrinolysis competitively. There are in vitro studies that show that it will bind to plasminogen

receptors<sup>31</sup> and to fibrin<sup>32</sup> and that it will inhibit plasminogen activation.<sup>14</sup> One attempt to show that Lp(a) lipoprotein does bind to plasminogen receptors in vivo, however, proved negative.<sup>33</sup> There have been three previous studies in which in vivo evidence of an effect of Lp(a) lipoprotein on thrombolysis has been sought with the clinical outcome of patients undergoing thrombolytic treatment for acute myocardial infarction as the model.<sup>34-36</sup> In none of these reports was streptokinase used. Nor was the electrocardiographic response investigated. These studies were small, involving only 20-50 patients, and because coronary angiography could not be undertaken without a clinical indication (as in our present study) they may have been confounded by selection bias. The results of these studies, like ours, showed no effect of Lp(a) lipoprotein on the patency of infarct-related coronary arteries.

We considered that the electrocardiographic response to thrombolytic treatment might provide an insight into the in vivo effect of Lp(a) lipoprotein in a larger, less biased series of patients than was possible with coronary angiography. This proved to be the case because it was possible to assess the rate of recovery of the ST segment elevation in 86% of a series of 135 patients. (The remainder could not be assessed as their electrocardiograms were unsuitable and showed abnormalities such as left bundle branch block and left ventricular hypertrophy). One factor limiting the return of the ST segment to the isoelectric line when thrombolytic treatment has been given is whether the ischaemic myocardium is successfully reperfused.<sup>19</sup> We therefore reasoned that were Lp(a) lipoprotein to interfere with thrombolysis a greater proportion of patients with high concentrations of serum Lp(a) lipoprotein at the time they received streptokinase would show a slower recovery in ST segment elevation. We found no evidence for this possibility in our study. Indeed, the patients with the more rapid decline of ST segments had a median concentration of Lp(a) lipoprotein that was one third greater than that of those with a slower response. This trend was close to significance and would have been so had our original hypothesis been that Lp(a) lipoprotein may have conferred some benefit. It is thus important to consider alternative hypotheses that might explain the results. One suggestion is that the coronary thrombosis, which forms in patients with high circulating Lp(a) lipoprotein concentrations, is particularly susceptible to lysis by streptokinase and thus reperfusion is more often evident in such patients. This may not be as improbable as it at first seems because Mao *et al* reported enhanced fibrinolysis in the presence of high Lp(a) lipoprotein concentrations in vitro.<sup>37</sup> This possibility is, however, not supported by the angiographic part of our study or the results of others.<sup>34-36</sup>

A second hypothesis to explain our electrocardiographic findings might be that they result, not so much from greater reperfusion of the myocardium in the patients with high

serum Lp(a) lipoprotein concentrations, but that they represent a greater degree of reperfusion injury in patients with low serum Lp(a) lipoprotein concentrations. If this were the case, its explanation might be that Lp(a) lipoprotein was acting to limit the extent of bleeding into the perinfarction zone after dissolution of the clot. Such bleeding leads to the morbid anatomical appearance of "red infarction"<sup>38</sup> and has been implicated as the cause of reperfusion injury (associated with prolonged elevation of ST segments due to persisting "current-of-injury"), slower recovery from myocardial injury, and eventually impaired ventricular remodelling.<sup>39,40</sup> Both coronary thrombolysis and red infarction can occur spontaneously during myocardial infarction, although they are more likely to do so if a thrombolytic agent has been given.

Thus although Lp(a) lipoprotein may be related to the risk of developing coronary atheroma, our findings do not exclude a possible beneficial effect during myocardial infarction. This suggests caution in the use of treatments aimed at lowering serum Lp(a) lipoprotein concentrations in patients at risk of coronary heart disease, because there may be advantages as well as disadvantages from a high concentration of circulating Lp(a) lipoprotein. Any in vivo effects it might have on coagulation are difficult to predict from in vitro experiments. We believe that serum Lp(a) lipoprotein concentrations should be correlated with the clinical outcome in larger trials of thrombolytic treatment.

This study was supported by an infrastructure award to PND and a Research Fellowship to ADM from the Northwest Regional Health Authority. We are grateful to the nurses and doctors of the casualty department and the coronary care unit of the Manchester Royal Infirmary for their contribution to this work and our consultant cardiology colleagues Drs DJ Rowlands, LC, Cotter, G Howitt and all the general physicians at the Royal Infirmary who allowed us to study patients under their care. We are indebted to Miss S Arrol for technical assistance and to Miss C Price for expertly typing the paper.

- 1 GISSI Study Group. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986;i:397-401.
- 2 ISIS 2 (Second International Study of Infarct Survival Collaborative Group). Randomised trial of intravenous streptokinase, oral aspirin, both or neither among 17 187 cases of suspected myocardial infarction. *Lancet* 1988;ii:349-60.
- 3 Wilcox RG, Von der Lippe G, Olson CG, Jensen G, Skene AM, Hampton JR. Trial of tissue plasminogen activator for mortality reduction in acute myocardial infarction. *Lancet* 1988;ii:525-30.
- 4 Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, *et al*. Thrombolysis in myocardial infarction (TIMI) trial, phase 1: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. *Circulation* 1987;76:142-54.
- 5 Van der Werf F, Arnold AER. For the European Cooperative Study Group for recombinant tissue type plasminogen activator. Intravenous tissue plasminogen activator and the size of infarcts, left ventricular function and survival in acute myocardial infarction. *BMJ* 1988;297:1364-79.
- 6 Marino P, Zanolli L, Zardini P. On behalf of the Gruppo Italiano per lo Studio della Streptochinasi nell Infarto Miocardico (GISSI). Effect of streptokinase on left ventricular modelling and function after myocardial infarction. *J Am Coll Cardiol* 1989;14:1149-58.
- 7 White HD, Norris RM, Brown MA, Takayama M, Maslowski A, Bass HM, *et al*. Effect of intravenous streptokinase on left ventricular function and early survival after acute myocardial infarction. *N Engl J Med* 1987;317:850-5.
- 8 AIMS Trial Study Group. Effect of intravenous APSAC on mortality after acute myocardial infarction: preliminary report of a placebo-controlled clinical trial. *Lancet* 1988;i:545-9.
- 9 ISIS 3. A randomised comparison of streptokinase versus tissue plasminogen activator versus anistreplase and of

- aspirin plus heparin versus aspirin alone among 41 299 cases of suspected acute myocardial infarction. *Lancet* 1991;229:753-70.
- 10 Durrington PN, Ishola M, Hunt L, Arrol S, Bhatnagar D. Apolipoprotein (a), A1 and B and parental history in men with early onset ischaemic heart disease. *Lancet* 1988;i: 1070-3.
- 11 Armstrong VW, Cremer P, Eberle E, Manke A, Schulz EF, Wieland H, *et al.* The association between serum Lp(a) concentration and angiographically assessed coronary atherosclerosis. Dependence on serum LDL levels. *Atherosclerosis* 1986;62:249-57.
- 12 Dahlen GH, Guyton JR, Altar MD, Farmer JA, Kautz JA, Gotto AM. Association of levels of lipoprotein Lp(a), plasma lipids and other lipoproteins with coronary artery disease documented by angiography. *Circulation* 1986; 74:758-65.
- 13 MacLean JW, Tomlinson JE, Kuang W-J, Eaton DL, Chen EY, Fless GM, *et al.* cDNA sequence of human apolipoprotein (a) is homologous to plasminogen. *Nature* 1987;300:132-7.
- 14 Hajjar KA, Gavish D, Breslow JL, Nachman RL. Lipoprotein (a) modulation of endothelial surface fibrinolysis and its potential role in atherosclerosis. *Nature* 1989;339:303-5.
- 15 Edelberg J, Pizzo SV. Why is lipoprotein (a) relevant to thrombosis. *Am J Clin Nutr* 1992;56:791S-2S.
- 16 MBewu AD, Durrington PN, Bulleid S, Mackness MI. The immediate effect of streptokinase on serum lipoprotein (a) concentration and the effect of myocardial infarction on serum lipoprotein (a), apolipoprotein A; and B, lipids and C-reactive protein. *Atherosclerosis* 1993;103:65-71.
- 17 Saran RK, Been M, Furniss SS, Hawkins T, Reid DS. Reduction in ST segment elevation after thrombolysis predicts either coronary reperfusion or preservation of left ventricular function. *Br Heart J* 1990;64:113-7.
- 18 Hogg KJ, Hornung RS, Howie CA, Hockings N, Dunn FG, Hillis WS. Electrocardiographic prediction of coronary artery patency after thrombolytic treatment in acute myocardial infarction; use of the ST segment as a non-invasive marker. *Br Heart J* 1988;60:275-80.
- 19 Willems JL, Willems RJ, Willems GT, Arnold AER, Van der Werf F, Verstraete M. For the European Cooperative Study Group for recombinant tissue type plasminogen activator. Significance of initial ST segment elevation and depression for the management of thrombolytic therapy in acute myocardial infarction. *Circulation* 1990;82:1147-58.
- 20 Selvester RH, Wagner JO, Rubin HB. Quantitation of myocardial infarction size and location by electrocardiogram and vector cardiogram. In: Snellin HA, ed. *Boerhave course in quantitation in cardiology*. The Netherlands: Leyden University Press, 1972:31-6.
- 21 Wagner GS, Freye CJ, Palmeri ST, Roark SF, Stack NC, Ideker RE, *et al.* Evaluation of a QRS scoring system for estimating myocardial infarct size. *Circulation* 1982;65: 242-50.
- 22 Mackness MI, Durrington PN. Lipoprotein separation and analysis for clinical studies. In: Converse CA, Skinner ER, eds. *Lipoprotein analysis—a practical approach*. Oxford: Oxford University Press, 1992:1-42.
- 23 MBewu AD, Bhatnagar D, Durrington PN, Hunt L, Ishola M, Arrol S, *et al.* Serum lipoprotein (a) in patients heterozygous for familial hypercholesterolaemia, their relatives and unrelated control populations. *Arteriosclerosis* 1991;11:940-6.
- 24 Srinivasan SR, Dahlen GH, Jarpa RA, Webber LS, Bevenson GJ. Racial (black white) differences in serum lipoprotein (a) distribution and its relation to parental myocardial infarction in children. Bogalusa heart study. *Circulation* 1991;84:160-7.
- 25 Seed M, Hopplcher MD, Reaveley D, McCarthy S, Thompson G, Boerwinkle E, Utermann G. Relation of serum lipoprotein (a) concentration and apolipoprotein (a) phenotype to coronary heart disease in patients with familial hypercholesterolaemia. *N Engl J Med* 1990;322: 1494-9.
- 26 Rosengren A, Wilhelmsen L, Eriksson E, Risberg B, Wedel H. Lipoprotein (a) and coronary heart disease, a prospective case-control study in a general population sample of middle-aged men. *BMJ* 1991;301:1248-51.
- 27 Jauhainen M, Kastein P, Ehnholm C, Frick MH, Manhtari M, Manninen V, Huttenen JK. Lipoprotein (a) and coronary heart disease risk: a nested case-control study of the Helsinki heart study participants. *Atherosclerosis* 1991;89:59-67.
- 28 Haffner SM, Moss SE, Klein BE, Klein R. Lack of association between lipoprotein (a) concentrations and coronary heart disease mortality in diabetes: the Wisconsin epidemiologic study of diabetic retinopathy. *Metabolism* 1992;41:194-7.
- 29 Maeda S, Abe A, Seishima M, Makino A, Noma A, Kawade M. Transient changes of serum lipoprotein (a) as an acute phase protein. *Atherosclerosis* 1989;78: 145-50.
- 30 Gavish D, Azrolan N, Breslow JL. Plasma Lp(a) concentration is inversely correlated with the ratio of Kringle IV/Kringle V encoding domains in the apo (a) gene. *J Clin Invest* 1989;184:2021-7.
- 31 Gonzalez-Gronow M, Edelberg JM, Pizzo SV. Further characterisation of the cellular plasminogen binding site. Evidence that plasminogen 2 and lipoprotein (a) compete for the same site. *Biochemistry* 1989;28:2374-7.
- 32 Harpel PC, Gordon BR, Parker TS. Plasmin catalyses binding of lipoprotein (a) to immobilized fibrinogen and fibrin. *Proc Natl Acad Sci USA* 1989;86:3847-51.
- 33 Correc P, Kostner GM, Burtin P. A comparative study of the localisation of plasminogen and apolipoprotein (a) in human carcinomas. *Thromb Res* 1990;58:213-20.
- 34 Von Hodenberg E, Kreutzer J, Hautmann M, Mordt T, Kubler W, Bode C. Effects of lipoprotein (a) on success rates of thrombolytic therapy in acute myocardial infarction. *Am J Cardiol* 1991;67:1349-53.
- 35 Armstrong VW, Neubauer C, Schutz E, Tebbe U. Lack of association between raised serum Lp(a) concentrations and unsuccessful thrombolysis after acute myocardial infarction. *Lancet* 1990;336:1077.
- 36 Tranchesi B, Filho RS, Vinagre C, Carmamelli B, Barbosa V, Gebara V, *et al.* Lipoprotein levels do not influence the outcome of TPA therapy in acute myocardial infarction. *Ann Haematol* 1991;62:141-2.
- 37 Mao SJT, Tucci MA. Lipoprotein (a) enhances plasma clot lysis *in vitro*. *FEBS Lett* 1990;267:131-4.
- 38 Davies MJ. Successful and unsuccessful coronary thrombolysis. *Br Heart J* 1990;61:381-4.
- 39 Poole-Wilson PA, Iles RA. Ischaemia, hypoxia and reperfusion. In: Cohen RD, Lewis B, Alberti KGM, Denman AM, eds. *The metabolic and molecular basis of acquired disease*. London: Bailliere Tindall, 1990: 322-47.
- 40 Braunwald E, Kloner RA. The stunned myocardium: prolonged postischaemic ventricular dysfunction. *Circulation* 1982;66:1146-9.